. DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103951/5001

JUL 19 2002

Jeffrey N. Fellows
Director, Regulatory Affairs
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Fellows:

Your request to supplement your biologics license application (BLA) for Darbepoetin alfa to include a new indication, for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, has been approved. In addition, three new dosage strengths (150 µg, 300 µg and 500 µg) in the Albumin (Human) formulation have been approved for this indication.

The dating period for the new Darbepoetin alfa containing Albumin (Human) dosage strengths shall be 36 months from the date of manufacture when stored at 2 to 8°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available. The revised stability protocol to include these new dosage strengths is considered approved for the purpose of extending the expiration dating period of your drug product as specified in 21 CFR 601.12.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 601.27). On the basis of your commitment described in item 3 below, we are deferring the submission of your pediatric studies, under 21 CFR 601.27(b), until January 2003.

We acknowledge your written commitments of July 18, 2002 to provide the following:

**Chemistry Manufacturing and Controls:**

1. To establish a specification for the amount of oxidized Darbepoetin alfa in the Albumin (Human) formulation of the final product. The ——— Darbepoetin alfa species will be detected by ——— in accordance with analytical method ———

   a. To set an initial specification for lot release and stability at — % and submit a copy of the Certificate of Analysis with the specification by August 30, 2002.

b. To submit revised release specifications for the amount of oxidized Darbepoetin alfa in the final Albumin (Human) formulated product based upon the analysis of data obtained from 30 commercial lots of final material by July 30, 2003.

**Clinical:**

2. To perform immunogenicity testing on serum samples obtained from approximately 2000 patients with chemotherapy induced anemia (CIA), evenly distributed between those receiving either the Albumin (Human) or the Polysorbate 80 formulation of Darbepoetin alfa. The data will be obtained from the studies specified in your letter of July 18, 2002. Immunogenicity testing will be performed using the more sensitive assays developed under your commitment to the original BLA (STN103951/0), for studies that are ongoing, not yet initiated, and where retention serum samples are available. The results will be analyzed to establish the overall incidence of immune responses with additional exploratory analyses to identify associations between immune responses and various clinical factors. The analytic plan for analysis of these data will be submitted by December 30, 2002. You commit to completing the antibody testing, submitting the results, and filing revised draft labeling by July 31, 2004.

3. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Darbepoetin alfa in pediatric patients in a ——— study conducted ———

a. The study will be completed (last patient exited) by September 2002, and the final clinical study report will be submitted to CBER in January 2003.

b. Following our evaluation of the PK and PD data, you have agreed to meet with us to discuss and evaluate the appropriateness of an additional pediatric study to identify a safe and effective dose for the use of Darbepoetin alfa in pediatric patients. If agreement is reached that an additional study is warranted, you commit to developing a protocol, obtaining our agreement on the study design and initiating this study by September 2003.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling materials with FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448.

Final printed advertising and promotional labeling materials should be submitted at the time of initial dissemination, accompanied by FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

This information will be included in your biologics license application file.

Sincerely yours,

Amy Rosenberg, M.D.
Director
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Evaluation and Research

Patricia Keegan for Dr. Weiss

Karen D. Weiss, M.D.
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